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Title Page

The Effects of Dexamethasone on Sleep in Young Children with Acute Lymphoblastic Leukemia

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Key words: cytokines; psychology; acute lymphoblastic leukemia

Highlights

- Daytime naps /night time sleep increase with dexamethasone
- Sleep complaints are common in children with leukemia
- Fatigue is a common complaint during chemotherapy

Abstract:

Purpose: Corticosteroids, which are a mainstay in the treatment of acute lymphoblastic leukemia (ALL), have a well documented adverse effect on sleep. We sought to characterize the effects of dexamethasone on sleep over an entire 28-day treatment cycle using actigraphy, an objective measure of sleep.

Methods: The sleep of twenty-five children, ages 2-9 (mean 4.5 years) with ALL treated with dexamethasone were evaluated during maintenance chemotherapy using a within subject experimental design, actigraphy, and standardized questionnaires to assess sleep, sleep problems and fatigue.

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Results: During the 5 days of dexamethasone treatment, sleep time increased during the night (535 vs 498 minutes; P=.004) and daytime napping increased the following day (14 vs 0 minutes; P=0.002), and the number of wake episodes during the night was lower (14 vs 20; P=<.001). Though, when assessed individually, sleep onset time, efficiency and wake after sleep onset, during the night were unchanged during dexamethasone treatment, when the cumulative effect of all of these factors was assessed, there was a statistically and clinically significant increase in nighttime sleep duration during dexamethasone treatment.

Conclusions: During the 5 days of treatment with dexamethasone, young children with ALL increase their nighttime sleep as well as their daytime napping. The increases in sleep duration return to baseline 1 day after the discontinuation of dexamethasone.

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Introduction:

Corticosteroids are a mainstay in the treatment of children with Acute Lymphoblastic Leukemia (ALL) during several phases of therapy, though the timing, dose, and choice of corticosteroids have changed over time based on clinical trials [1]. The adverse behavioral effects of corticosteroids are well documented and include: fatigue, irritability, insomnia, hypersomnia, mood lability, psychosis, and fluctuating levels of alertness. The physiologic mechanisms underpinning these problems are not fully understood [2-9]. In North America, dexamethasone is currently used during the induction, delayed intensification and maintenance phases of chemotherapy in most ALL protocols in doses that range from 6-12 mg/m^2 /day X 5-28 day pulses. Most children treated for ALL in North America receive dexamethasone for over half of their 2-3 years of treatment [1].

The adverse effects of corticosteroids on sleep in children with ALL have been recognized since prednisone was first used for the treatment of ALL. Insomnia, hypersomnia and fatigue are all commonly reported adverse side effects, which have been attributed to treatment with corticosteroids [3-9]. A study by Hinds [6] was the first to use actigraphy, providing an objective measure of sleep comparing sleep during the five days before dexamethasone (dex off), to the next five days, on dexamethasone 6-12mg/m^2 /day (dex on). Dexamethasone treatment lead to an increase in: sleep duration, actual sleep minutes, total daily sleep minutes, and total daily napping minutes; and a decrease in the number and duration of nocturnal awakenings. The parents of the children under study described increases in their child's fatigue while on dexamethasone for all risk groups. In other questionnaire-based studies of sleep in children with ALL, the majority of children (74-97%) exhibited a wide range of sleep problems which included increases in: bedtime resistance, sleep anxiety, and nighttime awakenings both while

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on and off dexamethasone [5, 9]. An incremental increase in daytime fatigue during treatment with dexamethasone has been noted by Yeh [8] in studies of children with cancer, though the cause for the increased fatigue is not understood. The goal of this study was to evaluate the changes in sleep that occurred over a 28-day maintenance cycle in children with ALL.

Methods:

English speaking children ages 2-9 years in maintenance chemotherapy with dexamethasone for ALL treated at Children's Hospital of Minnesota were recruited for participation. Consent was obtained from all parents of participants and assent from all children older than seven years of age. The institutional review board of Children's Hospital of Minnesota approved this study. All patients were treated according to standard Children's Oncology Group (COG) protocols (Table 1) and received oral dexamethasone (6mg/m^2/day divided into 2 doses) on days 1-5 of maintenance chemotherapy.

After consent/assent was obtained, children were fitted with an actigraph. An actigraph is a wristwatch-sized linear accelerometer that estimates sleep and wakefulness based on the measurement of movement using a validated algorithm [11]. The MicroMini Motionlogger sleep watch (Ambulatory Monitoring Inc, Ardsley, NY, USA) was used in this study. Data were analyzed in one-minute epochs, in the zero crossing mode, using the Sadeh algorithm [11] for staging wake and sleep. The actigraph was placed on the non-dominant wrist and the child and the parents were instructed to remove the actigraph only during bathing or vigorous physical activity. Sleep log data were also collected. Sleep onset and wake time were defined by actigraphic criterion. Sleep efficiency was defined as sleep time/ (sleep onset time-wake time); wake episodes

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during sleep were defined as the number of blocks of continuous wake during the night time sleep interval; wake after sleep onset (WASO) was defined as number of minutes of wake between sleep onset and morning wake-up time; daytime naps were defined as minutes of sleep recorded between wake time in the morning and sleep onset time the following evening. Activity count is a measure of the amount of movement occurring during a one-minute epoch. When night time sleep is defined in this manner, by actigraphic criteria, sleep onset latency, WASO, and early morning awakenings when the child remains in bed, will not be included in the calculation of minutes of sleep and will be significantly shorter than time in bed.

Sleep was monitored continuously in each subject for a complete 28-day chemotherapy cycle. This allowed the comparison of how an individual child's sleep changed over the course of the 28-day chemotherapy treatment cycle. Each child's sleep during the 5 days on dexamethasone was compared to the same child's sleep off dexamethasone; permitting each child to serve as their own control. This is necessary if one is to make a meaningful comparison of the effect of a drug (dexamethasone) on sleep, because of the great deal of inter individual variability in children's sleep.

Dexamethasone has a long biologic ½ life. If one considers the ½ life to be 36-54 hours for dexamethasone, the activity of dexamethasone left in the body will be only 1/32 of original dosage after 5 half-lives, which is 10 days [12]. For this reason, sleep was compared when the child was taking dexamethasone days 1-5 (dex on), during dexamethasone washout, days 6-15 (the 10 days immediately after dexamethasone was taken but when there may still be biologic

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effects of dexamethasone), and during the 10 days after the last dose of dexamethasone days 16-28 (dex-off) when all biologic effects of dexamethasone are presumed to be over.

Parent proxy assessment of sleep problems were assessed once for each child, at the beginning of a chemotherapy cycle before beginning dexamethasone treatment, using the Children's Sleep Habits Questionnaire (CSHQ) [13, 14]. The CSHQ has been used previously to evaluate for sleep problems in children with ALL [5, 9]. The CSHQ is a widely used proxy measure of children's sleep that is based on the parent's assessment of their child's sleep problems. It has been validated in children age 4-10 years and has been used extensively in the study of parent reported sleep problems in young children who are normally developing [13, 14], and in children with sleep disorders [13, 14], autism [15], epilepsy [16], ALL [5] and children with neurodevelopmental delays [15].The CSHQ is a 56 item multiple choice questionnaire that is summed into 8 subscales and a total score. In the validation studies, a cut off total CSHQ score of 41 differentiated a community group from a clinically referred sleep disordered group with a sensitivity of 0.8 and a specificity of 0.72 [13].

Fatigue was assessed only on day 1, at the beginning of the maintenance cycle before beginning dexamethasone using the Parents Fatigue Scale (PFS). This is a 17 item measure of the parent's perception of their child's fatigue scored on a 5-point Likert scale. The PFS is a validated measure of parent's assessment of their child's fatigue, in children with cancer [17].

Statistical methods:

The within subject experimental design of this study allowed each child to serve as their own control for the analysis of the actigraphic data. To examine if dexamethasone treatment was

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associated with sleep, we compared the actigraphic data for each child starting 10 days after their last dose of dexamethasone dex-off (days 16-28) to their sleep parameters on dexamethasone dex-on (days 1-5). We described normally distributed data using means (SD) and made comparisons with paired t-tests. For non-normally distributed data, median, ranges were chosen to describe the data and the Wilcoxon Signed Rank Test was used for paired comparisons.

Patient Characteristics:

Over the two years the study was open, 53 children/families were approached to participate; 17 families declined. There were no specific exclusion criteria of co-existing sleep problems, or co-morbid diseases which may affect sleep, such as attention deficit disorder. Actigraphs were placed on 36 children; 1 actigraph was lost, 4 actigraphs malfunctioned, and 6 actigraphs were not worn for an adequate duration. Adequate actigraphic data was collected from 25 children. The subjects included in this report are the 25 children ages 2-9 years, who were treated with dexamethasone for whom adequate actigraphic data were collected. This group was chosen to provide as homogeneous a sample as possible to understand the relationship between sleep and dexamethasone in young pre adolescent children with ALL. The demographic data of the patients is shown in Table 1: median age was 4.5 years (2-9 years); 56% female and 44% males; as expected from this age range 24 patients (96%) were treated on standard-risk ALL protocols and one was treated on high-risk protocol. In regards to effects on sleep, during maintenance chemotherapy there is no significant difference between these treatment protocols. In addition to the dexamethasone all patients received mercaptopurine, methotrexate and vincristine, and all received intrathecal methotrexate on day 1 of the maintenance phase of chemotherapy.

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None of the children on this study were taking chronic medication for sleep. One child received midazolam for conscious sedation for the lumbar puncture on day 1 of the study, one child was given melatonin on day 1 of the study, and one child was given melatonin on days 20-28 of the study.

Results:

Actigraphy:

Figure 1 graphically shows day-by-day median values for: night sleep time and day sleep time (naps) for the 28 days recorded on the actigraph for the entire cohort. Table 2 describes the same data in addition to: sleep onset time, WASO, sleep efficiency, wake episodes/night, and activity counts daily for days 1-5 on dexamethasone treatment (dex-on), day 6 (1 day after dexamethasone treatment was completed), days 7-15 off dexamethasone (dex washout), and days 16-28 off dexamethasone, (dex- off). Table 3 compares the median actigraphic measures during the 5 days on dexamethasone, days 1-5; to days 16-28, off dexamethasone (dex-off). Figure 2 shows a typical 28 day actigraphic recording from one of the children in the study. Movement is scored in 1-minute epochs. Sleep is noted by red underscore, nighttime sleep noted by green shading with red underscore; daytime sleep red underscore. Purple underscore indicates the actigraph is off subject.

Nighttime sleep parameters:

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During the 5 days on dexamethasone treatment the median nighttime sleep duration was longer, 535 (SD 71) minutes vs. 498 (SD 47.5) for dexamethasone off days (p=0.004); and the number of wake episodes each night was lower,14 (SD 7.5) awakenings/night vs. 20 (SD 6.9) awakenings for dexamethasone off days (p<.001 (Table 3). During night 3 of dexamethasone treatment, nighttime sleep duration was 556 minutes; the longest duration of sleep during the entire 28-day study period, which is 58 minutes longer than the mean nighttime sleep duration for off dexamethasone days. When evaluated individually sleep onset time, sleep efficiency and WASO did not change significantly over the entire 28-day treatment cycle (Table 2&3). However, the cumulative effect of all three of these factors taken together, lead to a clinically and statistically significant increase in nighttime sleep duration. Wake time in the morning was unchanged when comparing on and off dexamethasone days.

Daytime sleep/wake parameters:

When off dexamethasone, only 2 children of the 25 studied were regularly taking naps, the other children had largely given up regular daytime napping. Most of the children resumed regular napping during the 5 days of dexamethasone treatment and on day 6, the day after finishing dexamethasone treatment (Figure 1, Table 2&3). The median number and duration of daytime naps was 0, during days 16-28 off dexamethasone. However, during the 5 days on dexamethasone treatment napping was the rule, with most children napping 2 times a day, range (0-5); with a median duration of 14 minutes/day, range (0-99 minutes) (p<.002) . Daytime sleep (naps) increased from 2 minutes on day 1, to 30 minutes on day 4. On day 5 (the day of the last dose of dexamethasone) and day 6 (the day after the last day of dexamethasone)

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daytime sleep remained increased at 13 and 12 minutes; before returning to the baseline levels of no daytime sleep for the remainder of the treatment cycle.

During dexamethasone treatment, mean activity counts/minute during the day progressively decreased from baseline levels 238 when off dexamethasone to 211 on day 5 of dexamethasone treatment, $p<.001$. Activity counts gradually rebounded after dexamethasone was discontinued; returning to baseline levels on day 8, 3 days after dexamethasone was discontinued.

Total sleep time:

Children increased their total time asleep during the 5 days of dexamethasone treatment compared to total sleep time off dexamethasone. Daytime napping, which began on day 1 and continued until day 6, did not lead to a later sleep onset time, nor a decrease in sleep efficiency. Rather, nighttime sleep duration was increased during the 5 days of dexamethasone treatment when children were taking their daytime naps.

Sleep during days 6-15 dexamethasone washout period

Sleep during days 6-15 appeared to be intermediate between sleep during dexamethasone treatment days 1-5, and when all of the biologic effects of dexamethasone were likely over on days 16-28. Nighttime sleep duration, wake episodes from sleep, number and duration of

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daytime naps were all intermediate between sleep/wake values while on dexamethasone and after dexamethasone had been off for greater than 10 days.

Sleep questionnaires:

Parents commonly reported sleep problems in their children. Table 4 describes the results of the CSHQ compared to healthy population norms reported by Owens [13, 14] and to other children with ALL reported by Litsenburg [5]. On the CSHQ, 60.9% of the children with ALL scored in the problem range (CSHQ>41). The parent proxy reported sleep problems were: bedtime resistance, sleep duration, sleep anxiety, night awakening and daytime sleepiness. These were the same problem areas noted by Litsenburg in a study 17 children with ALL from the Netherlands. Sleep problems were measured only during the dexamethasone off condition, so the effect of dexamethasone on sleep problems could not be assessed in this study.

Fatigue:

Twenty-four percent (PFS score range 41.75 to 54) of parents rated their child as fatigued, according to the established PFS mean score of 41 and higher. The total fatigue score for PFS were similar to that reported in Hockenbury's study of fatigue in children with ALL [17]. Fatigue was measured only during the dexamethasone off condition, so the effect of dexamethasone on fatigue could not be assessed in this study.

Discussion:

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Young children with ALL during chemotherapy sleep differently during days 1-5 at the beginning of their chemotherapy cycle, compared to their sleep off dexamethasone at the end of their treatment cycle. Similar to the findings of the Hind's study [6], during days 1-5, when the children were receiving dexamethasone they slept longer at night and awakened less frequently; and most resumed taking daytime naps, which had previously been discontinued. All of which suggests that these children were sleepier during their treatment with dexamethasone. These children's' daytime napping did not interfere with their nighttime sleep.

Sleep is a dynamic neurologic process, the result of a delicate balance of developmental, circadian, homeostatic and other factors. There is a great deal of inter-individual variability in different children's sleep at the same age, and there are developmental changes in a child's sleep over time; however, an individual child's sleep need is generally very consistent night to night. In this study all comparisons of sleep duration were made in the same child over 28 consecutive days minimizing the developmental changes that occur in children's sleep over time. This design optimizes the study's ability to identify changes in sleep on and off dexamethasone. Though other drugs in addition to dexamethasone were taken by each of the children per their treatment protocol as noted in Table 1, none of the other medications have shown a consistent effect on sleep, and none of the changes in sleep duration found in this study matched the timing of the other drugs that were administered. However, the relationship between the changes in sleep found in this study, and dexamethasone treatment are correlational, and though the timing of the changes fits best with the timing of dexamethasone treatment, methotrexate, vincristine and 6 mercaptopurine were all part of the chemotherapy these children received and may be factors contributing to the changes in sleep noted in this study.

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Two mechanisms have been suggested to understand the changes in sleep that occurs in young children during treatment with high dose dexamethasone. The effects could be mediated by the hypothalamic pituitary axis (HPA) and/or changes in cytokines and their effects on sleep. Corticosteroids affect sleep at multiple levels of the nervous system [18-22]. These effects are mediated by the direct effects of corticosteroids that can cause an increase in alertness or indirectly by feedback inhibition of the release of corticotrophin releasing hormone (CRH). Corticotrophin releasing hormone activates the locus cerouleus/norepinephrine system thereby increasing wakefulness, it's inhibition decreases wakefulness and increases slow wave sleep. This complex effect of the HPA on sleep may explain the apparently contradictory research and clinical findings noted in different studies of the effects of corticosteroids and sleep. Dexamethasone has been shown to increase alertness, leading to insomnia [21]; as well as to increase slow wave sleep and daytime sleepiness [22]. In clinical studies of children with ALL treated with corticosteroids, both insomnia and hypersomnia are reported as adverse side effects attributed to dexamethasone [2- 4]. Another potential mechanism for the effects of dexamethasone on sleep involves inflammatory cytokines. Tumor necrosis factor (TNF)-alpha, IL-1, and IL-6 are important in sleep regulation [23]. They are noted to be increased in adults and children with obstructive sleep apnea and sleep insufficiency, and are associated with daytime sleepiness. Tumor necrosis factor-alpha and IL-1 meet the criteria as sleep regulatory substances [24]. Single nucleotide polymorphism's of TNF-alpha and IL-6 are associated with disturbed sleep in children with ALL [25]. Tumor necrosis factor -alpha, IL-1, and IL-6 have also been identified as mediators of "sickness syndrome" in human and animal studies and are believed to be important factors mediating fatigue [25].

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These young children experienced both fatigue and sleepiness. Fatigue and sleepiness are related but clinically distinct phenomena. Sleepiness is understood as a propensity to sleep. Sleepiness can be measured objectively, ideally with a mean sleep latency study [26], though in this study actigraphy was used as a proxy measure of sleepiness. Fatigue is much more difficult to quantify. Fatigue is a multidimensional, subjective symptom, best defined through the use of validated questionnaires. There are no objective, physiologic measures of fatigue. Cancer related fatigue (CRF), is understood as a unique form of fatigue seen in individuals with cancer [27]. Cancer related fatigue is one of the most distressing and least understood symptoms of cancer. There are no pathophysioloic mechanisms recognized as causing CRF, nor are there any treatments available to relieve it. Cluster analysis of cancer symptoms typically show that CRF and sleep problems occur together [28], though the relationship between CRF and sleep is not understood. Sleep disruption has been proposed as a possible cause of CRF, and if true would provide a treatment approach to mitigate the fatigue. This study, though limited, does not support this causal relationship between CRF and sleep disruption, in children with ALL. This study did not demonstrate a deterioration of night time sleep during dexamethasone treatment. Though, sequential measures of fatigue were not made in this study, previous research [6,8] does suggest that fatigue increases sequentially during dexamethasone treatment in children with cancer. All of the children in this study were getting less sleep than recommended, during and after the dexamethasone treatment . The chronic sleep insufficiency these children were experiencing may be a factor which compounded the impact of dexamethasone on sleep

This study should be considered preliminary and has several important deficiencies in design and instrumentation that limit the conclusions that can be drawn from the data. Sleep was

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assessed using actigraphy, a proxy measure of sleep, not polysomnography. Actigraphy uses a validated algorithm to score wake or sleep based on the amount of movement in a one-minute epoch. Actigraphy cannot assess depth, stages, or cycles of sleep, and is not a good tool for evaluating short awakenings from sleep [30]. During dexamethasone treatment, movement decreased both during the day and less so during the night. The actigraph may have mis-scored waking epochs as sleep because of the decreased movement. This misclassification of wake without movement as sleep may falsely increase the amount of sleep recorded on the actigraph. Actigraphy has been validated as a tool to measure sleep against polysomnography in normal adults and children, but not in children with ALL. However, actigraphy has been used extensively in the study of sleep in adults and children with cancer. The questionnaires of sleep and fatigue were administered only once during this study, while children were off dexamethasone.

The practical implications of these findings in the care of children with ALL treated with dexamethasone is that young children appear to be sleepier during the 5 days of dexamethasone treatment and the day following treatment and should be given a longer opportunity for sleep, both at night and during the daytime. These changes in sleep could be due to an increase in the homeostatic drive to sleep induced by dexamethasone. Confirmation of these findings would require polysomnography, ideally with quantitative EEG to allow for the evaluation of slow wave activity. This could identify an increase in slow wave activity, which if present would be consistent with an increase in the homeostatic drive to sleep during treatment with dexamethasone.

Conclusion:

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During the 5 days of treatment with dexamethasone, children with ALL slept more. There was an increase in night time sleep duration, a decrease in the number of awakenings during the night, continued high sleep efficiency and the re-appearance of daytime napping, which had previously been discontinued. The daytime napping did not adversely affect the quality of the subsequent nighttime sleep. This sleep pattern ended 1 day after the discontinuation of dexamethasone. In these children, there was no indication that the quality of nighttime sleep was adversely affected by treatment with dexamethasone. This study demonstrates that in young children with ALL, nighttime sleep does not deteriorate during dexamethasone treatment, and the children become sleepier the next day. This finding suggests that the daytime sleepiness that is seen in children during treatment with dexamethasone is not caused by a deterioration of their nighttime sleep. If this is true then the daytime fatigue which often accompanies treatment with dexamethasone is not likely caused by nighttime sleep fragmentation. This is consistent with the thesis of Kim et al [30] of a shared biological mechanism underlying the psycho neurological symptoms of fatigue and sleep disorders in patients with cancer.

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Bibliography:

1) Margolin JF, Steuber CP, Poplack DG. Acute lymphoblastic leukemia. In :Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:538.
2) Stuart FA,Gegal TY, Keady S. Adverse psychological effects of corticosteroids in children and adolescents. Arch Dis Child.2005;90:500-506.
3) Harris JC, Carel CA, Rosenberg LA, et al.Intermittent high dose corticosteroid treatment in childhood cancer: Behavioral and emotional consequences. J Am Acad Child Psyc. 1986;25(1):120-124.
4) Drigan R, Spirito A, Gelber RD. Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. Med and Ped Oncol 1992;20:13-21.
5) Van Litsenburg RR,Huisman J, Hoogerbrugge P, et al. Impaired sleep affects quality of life in children during maintenance treatment for acute lymphoblastic leukemia:an exploratory study. Health Qual Life Outcomes 2011;9:25-32.
6) Hinds P, Hockenberry M, Gattuso J et al. Dexamethasone alters sleep and fatigue in pediatric patients with acute lymphoblastic leukemia. Cancer 2007;110:2321-30.
7) Vallance K, Liu W, Mandrell B, et al. Mechanisms of dexamethasone induced disturbed sleep and fatigue in pediatric patients receiving treatment for ALL. Eur J Cancer2010;46(10):1848-1855.
8) Yeh CH, Chiang YC, Yang CP et al. Clinical factors associated with fatigue over time in pediatric oncology patients receiving chemotherapy. Br J of Cancer 2008;99:23-29.
9) Zupanec S, Jones H, Stremler R. Sleep habits and fatigue of children receiving maintenance chemotherapy for ALL and their parents. J Ped Onc Nursing 2010;27:217-228.
10) Iglowstein I, Jenni O, Molinari L et al. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics 2003;111:302-307.

ACCEPTED MANUSCRIPT

11) Sadeh A, Alster J,UrbachD, et al. Actigraphically based automatic bedtime sleep-wake scoring: validity and clinical applications. J Ambul Monitor 1989;2:209-216.

12) Solimando D. Drug information handbook for oncology, 5 th ed. Hudson,Ohio:Lexi-Comp.2004:266.

13) Owens J,Spirito A, McGuinn M, The childrens sleep habits questionnaire (CSHQ):psychometric properties of a survey instrument for school aged children.Sleep 2000:23;1-9.

14) Owens J, Spirito A, McGuinn M et al. Sleep habits and sleep disturbance in elementary school aged children. J Dev Behav Ped 2000;21:27-36.

15) Adkins K, Molloy C, Weiss S, Reynolds A, Goldman S,Clemons T et al. Effects of a standardized pamphlet on insomnia in children with autism spectrum disorders.Pediatrics 2012:Suppl2: S139-144.

16) Larson AM, Ryther RC, Jennesson M, Geffrey AL, Bruno PL, Anagnos CJ,et al. Impact of pediatric epilepsy on sleep patterns and behaviors in children and parents. Epilepsia. 2012 Jul;53(7):1162-9.

17) Hockenbury M, Hinds P, Barrera P, Bryant R, Adams-McNeillj, Hooke C, et al. Three instruments to assess fatigue in children with cancer, the child,parent, and staff perspectives. J Pain Symptom Manage 2003;25:319-328.

18) Friess E, Tagaya T, Grethe C, et al. Acute cortisol administration promotes sleep intensity in man. Neuropsycopharmacology 2004;29:598-604.

19) Steiger A. Sleep and the hypothalamo-pituitary-adrenocorticalsystem. Sleep Med Rev2002;6:125-138.

20) Buckley T, Schatzberg A. Review:on the interactions of the hypothalamic-pituitary-adrenal axis and sleep:normal HPA axis activity and circadian rhythm,exemplary sleep disorders. J Clin Endo and Metab 2005;90:3106-3114.

Accepted Manuscript

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21) Meixner R, Gerhardstein R, Day R, et al. The alerting effcts of dexamethasone. Psychophysiol 2003:40;254-259.

22) Freiss E, Tagaya H, Grethe C, et al. Acute cortisol administration promotes sleep intensity in man. Neuropsychopharmacology 2004:29;598-604.

23) Krueger K, Rector D, Churchill L. Sleep and cytokines. Sleep Med Clinics 2007;161-169.

24) Vallance K, Yang J, Li J, et al. Disturbed sleep in pediatric patients with leukemia:the potential role on interleukin-6(-174GC) and tumor necrosis factor (-308GA) polymorphism. Onc Nursing Forum 2011;38:E365-372.

25) Bryant P, Trinder J, Curtis N. Sick and tired:does sleep have a vital role in the immune system? Nature Rev Immunology 2004;4:457-467.

26) Carskadon M, Dement B, Mitler M, et al. Guidelines for the multiple sleep latency test (MSLT): A standard measure of sleepiness.Sleep1986;9:519-24.

27) Berger A, Abernathy A, Atkinson A, et al. Cancer-related fatigue.J Natl Comp Canc Netw.2010;8:904-31.

28) Beck S, Dudley W, Barsevick A. Pain, sleep disturbance, and fatigue in patients with cancer: using a mediation model to test a symptom cluster. Oncol Nurs Forum 2005;32:E48–55.m

29) Kanady J, Drummond S, Mednick S. Actigraphic assessment of a polysomnographic-recorded nap:a validation study. J Sleep Res 2011;20:214-222.

30) Kim H, Barsevick A, Fang C, et al. Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. Cancer Nursing 2012:35;E1-E20.

Figure 1: Nighttime sleep and daytime sleep (naps) during 28 days of the maintenance chemotherapy cycle.

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Dexamethasone treatment (6 mg/m^2/day) divided twice a day on days 1-5.

All data expressed as median values of the entire study cohort.

Figure 2: This is a typical twenty-eight day actigraph recording from one of the children in the study. Movement is scored in 1-minute epochs. Sleep is noted by red underscore, Nighttime sleep noted by green shading with red underscore; daytime sleep red underscore. Purple underscore indicates the actigraph is off subject.

Table 1. Demographic s

	n	**%**
Total	25	
Age	Median 4.5 years	(Range 2-9 years)
Females	14	56%
Males	11	44%
ALL Risk Group:		
Standard Risk	24	96%
High	1	4%
COG Protocol 1991	3	12%
COG Protocol AALL0331	21	84%
COG Protocol AALL0232	1	4%
Chemotherapy Used During Study Period:		
Dexamethasone 6 mg/m^2 PO Days 1-5	25	100%
Vincristine 1.5 mg/m^2 IV Day 1	25	100%
Mercaptopurine 75 mg/m^2 PO	25	100%

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Days 1-28		
Methotrexate 20 mg/m^2 PO Days 8, 15, 22	25	100%
Methotrexate (age based) Intrathecal Day 1	25	100%

ALL = Acute Lymphoblastic Leukemia; COG = Children's Oncology Group; IV = Intravenous;

PO = Oral Intake

Table 2 : Day by day measures of sleep and activity during the 28 day chemotherapy cycle

Days	1	2	3	4	5	6	7-15	16-28
Dexamethasone 6mg/m^2/day	Dex-On	Dex-On	Dex-On	Dex-On	Dex-On	Dex wash-out		Dex-Off
Sleep Onset time - median	21:20	21:27	21:10	21:56	21:37	21:35	22:03	22:00
Night sleep time – minutes, mean (SD)	517.9 (79.6)	521.5 (76.1)	556.1 (95.2)	539.6 (103.5)	543.6 (105.5)	510.0 (80.4)	494.8 (63.4)	498.3 (47.5)
Wake after sleep onset –minutes, median (range)	30 (0,136)	41 (5,224)	48 (11, 216)	49 (9, 206)	35 (9, 152)	31 (0, 223)	47 (16, 139)	64 (21, 123)
Sleep efficiency (%), mean (SD)	92.5 (6.5)	88.8 (8.7)	88.5 (9.5)	89.1 (9.0)	91.9 (7.4)	90.9 (8.4)	88.8 (5.8)	88.4 (5.4)
Wake episodes/night (#) , mean (SD)	12.5 (8.8)	15.9 (10.6)	15.1 (10.0)	15.8 (10.4)	12.0 (8.3)	12.2 (9.4)	18.0 (7.6)	20.0 (6.9)
Day sleep time – minutes , median (range)	2 (0,105)	11 (0,122)	21 (0,139)	30 (0, 221)	13 (0,118)	12 (0,238)	0 (0,81)	0 (0,100)
Daytime activity counts (#) , mean (SD)	229.9 (27.4)	215.7 (28.8)	205.2 (32.8)	201.5 (30.4)	202.4 (34.3)	221.7 (16.4)	233.7 (19.6)	238.3 (21.6)

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Table 3: Comparison of Actigraph Data between the 5 days on treatment with Dexamethasone and the 13 days at the end of the recording interval when off Dexamethasone

	Dex – On (Days 1-5) n=25	**Dex - Off (Days 16 -28) n=25**	**p-value[a]**
Sleep onset & wake-up time			
Sleep onset time **Median (Range)**	21:29 (18:50,1:25)	22:00 (18:54, 23:38)	0.19
Wake-up time **Median (Range)**	7:19 (5:03, 9:50)	7:46 (4:45, 9:38)	0.90
Sleep related parameters			
Night sleep time –minutes , **Mean (SD)**	535.4 (71.0)	498.3 (47.5)	0.004
Sleep efficiency %, **Mean (SD)**	90.1 (6.8)	88.4 (5.4)	0.12
WASO –minutes, **Median (Range)**	41 (15, 145)	64 (21,123)	0.08
Wake episodes, **# Mean (SD)**	14.3 (7.5)	20.0 (6.9)	<0.001
Daytime			
Activity counts , **# Mean (SD)**	211.2 (24.0)	238.3 (21.6)	<0.001
Sleep time ,minutes **Median (Range)**	14 (0, 99)	0 (0,100)	0.002
Sleep episodes , **# Median (Range)**	2 (0,5)	0 (0,4)	<0.001

WASO – wake after sleep onset

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Table 4: Child's Sleep Habits Questionnaire (CSHQ) comparison with literature

Subscale	**Our results**		**Owens results (Mean) [13]**			
	N=25					**Litsenburg [5]**
	Median (range)	**Mean (SD)**	**Total n=494**	**Non-problem sleepers***	**Problem sleepers***	**ALL (n=17)**
1. Bedtime resistance	8.0 (4, 15)	9.3 (3.3) ◊	7.07	6.67	10.44	6.38 ◊
2. Sleep onset delay	1 (1, 4)	1.5 (0.8)	1.27	1.18	2.2	1 ◊
3. Sleep duration	4 (3, 8)	4.3 (1.5) ◊	3.45	3.27	4.89	3
4. Sleep anxiety	5.5 (2, 11)	6.0 (2.3) ◊	4.89	4.74	9.00	5 ◊
5. Night wakings	5 (3, 7)	4.7 (1.4) ◊	3.53	3.43	5.61	4 ◊
6. Parasomnias	7.5 (7, 13)	8.1 (1.6)	8.14	7.95	9.53	9
7. Disordered breathing	3 (3, 4)	3.1 (0.3)	3.26	3.23	5.50	3
8. Daytime sleepiness	12 (8, 20)	12 (3.0) ◊	9.63	9.16	13.95	11

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Total CSHQ score	44 (31, 58)	45 (7.8)	38.8	/	/	/

Notes: Owens' study sample was a group of 494 elementary school children, grades kindergarten through fourth

◊ Significantly different from the scores from 494 children aged 4 to 11 years studied by Owens.

A total CSHQ score of 41 is a sensitive clinical cut-off for identification of probable sleep problems. The mean total score was **45** for our patients, **(60.9%)** had a total score greater than 41.

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